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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,333	11/14/2003	Anastasia Khvorova	DHARMA 0100-US2	6379

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.**	**Applicant(s)**	
	10/714,333	KHVOROVA ET AL.	
	Examiner	**Art Unit**	
	Janet L. Epps-Ford	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-6,8 and 19-37 will remain rejected under 35 USC 112, 1st for the reasons of record*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached note.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit: 1633

Continuation of 5. Applicant's reply has overcome the following rejection(s): The rejection of claims 2-5 under 35 USC 112, 2nd paragraph; and the rejection of claims 2 and 19 under 112, 1st (written description).

DETAILED ACTION

Response to Arguments

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Those rejections set forth in the prior Office Action, but not repeated in the instant Office Action have been withdrawn in response to Applicant's amendment and/or arguments.

Claim Rejections - 35 USC § 112

3. The rejection of claims 2-5 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in response to Applicant's amendment. The rejection of claims 2 and 19 under 35 USC 112, 1st paragraph for lack of written description is withdrawn.

4. Claims 1-6, 8, and 19-37 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record.

Applicant's arguments filed 7-31-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that "the examiner has not shown what if any experimentation is necessary to practice the claims as amended" (see page 16 last paragraph of Applicant's response), instead "the examiner

appears to take issue with whether applying the claims over their breadth would allow for the selection of siRNA of a specific functionality. " Additionally, Applicants provided a clarification of the various non-target criterion that are described in the specification as filed (see page 17 1st paragraph of Applicant's response), and further stated that "rationally designed siRNA in its broadest sense could in theory have any degree of absolute functionality."

Moreover, page 19, 2nd paragraph states:

> As the specification teaches, because the invention as claimed in claim 2 is directed to a method for selecting siRNA based on criteria that increase the likelihood of functionality there may be instances when the siRNA that are suggested do not, when placed into an *in vitro* system have the desired level of functionality. However, the very passage cited by the Examiner teaches that in these circumstances a person of ordinary skill could simply try another one of the formulas. Thus, there is no undue experimentation or any experimentation in the selection process.

According to Applicant's initial traversal of the instant rejection, "the examiner has not shown what if any experimentation is necessary to practice the claims as amended." However, the above passage indicates that it is possible to use the criterion suggested by Applicants, and still not produce a siRNA with the desired functionality after placing the siRNA into an *in vitro* system. This statement suggests that there is a certain level of unpredictability associated with the behavior of the siRNA in an *in vitro system,* in comparison to the predictions made using the various parameters set forth in the specification as filed (or recited in the instant claims). According to the above statement by Applicants, if a siRNA does not have the desired functionality after applying the criteria, the person of ordinary skill could simply try another one of the formulas.

However, the specification as filed suggests that even if using two different criteria, it is possible to produce conflicting results, leading to further experimentation with no guarantee of producing a functional siRNA, see for example page 26, lines 18-29 of the specification as filed, wherein it is stated:

> is, for instance, more stringent. Alternatively, it is conceivable that analysis of a sequence with a given formula yields no acceptable siRNA sequences (*i.e.* low SMARTscores™). In this instance, it may be appropriate to re-analyze that sequences with a second algorithm that is, for instance, less stringent. In still other instances, analysis of a single sequence with two separate formulas may give rise to conflicting results (*i.e.* one formula generates a set of siRNA with high SMARTscores™ while the other formula identifies a set of siRNA with low SMARTscores™). In these instances, it may be necessary to determine which weighted factor(s) (*e.g.* GC content) are contributing to the discrepancy and assessing the sequence to decide whether these factors should or should not be included. Alternatively, the sequence could be analyzed by a third, fourth, or fifth algorithm to identify a set of rationally designed siRNA.

This passage suggests that the criteria set forth in the specification as filed, and as recited in instant claims 2 and 19, do not represent ***a proven set of criteria*** as required for the rational design of an siRNA, since the application of one or more of these criteria may or may not give you the desired result, or even give you conflicting results, and re-analysis with another algorithm may be required, or furthermore re-analysis with a third, fourth, or fifth algorithm may be required to identify a set of rationally designed siRNA. The above passage suggests the potential need for further experimentation in order to identify functional siRNA, wherein such guidance is beyond the scope of the instant disclosure.

As stated in the prior Office Action, due to the lack of clear guidance set forth in the specification as filed that for selecting functional and hyperfunctional siRNA according to the present invention, the skilled artisan would not have been able to practice the full scope of the claimed invention without undue experimentation since the skilled artisan would have to resort to unpredictable *de novo* experimentation without particular guidance from the specification as filed. There are a variety of suggestions given regarding the evaluation of particular non-target specific criterion, however the skilled artisan is not given clear and specific guidance as how to use these particular criteria for rationally designing a functional or hyperfunctional siRNA. Moreover, apart from further experimentation, without particular guidance from the specification as filed, there is no clear guidance for the selecting the particular criteria necessary for the rational design of siRNA.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 1, 6, 8, and 21-37 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description).

Applicant's arguments have been fully considered, but are not persuasive. Applicants traversed the instant rejection on the grounds Applicants have adequately

described both the use of non-target specific criterion and the specific criteria delineated in the specification are inventive. However, it is noted that the instant claims are not limited to those specific criteria recited in the specification. As stated in the prior Office Action, Applicant's own specification suggests that other criteria, not specifically disclosed are encompassed within the scope of the invention, for example at page 40, criteria I-VIII are described, however at lines 27-29, it states that "in an effort to improve selection further, all identified criteria, ***including but not limited to those listed in Table IV*** were combined into algorithms embodied in Formula VIII, and Formula IX." There are so many permutations to these formulas, it is unclear what other specific proven criteria Applicants are referring to, again, apart from further experimentation the skilled artisan would not be able to specifically pinpoint the particular parameter in these formulas that would be particularly useful for identifying the full scope of functional siRNA encompassed by the claims.

The instant claims are rejected for the reasons of record, and furthermore the instant claims are considered to lack a sufficient written description regarding the application of a "proven set of criteria that enhance the probability of identifying a functional or hyperfunctional siRNA." Due to the ambiguity associated with the disclosure (see pages 26, 40-41 and 53) regarding which particular criteria would yield the rationally designed siRNA according to the present invention, and the apparent need for further experimentation to identify the full scope of non-target specific criteria encompassed by the instant claims, it does not appear that Applicant's were in possession of the full scope of the invention at the time of the instant invention.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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JLE